(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016616 A1

(51) International Patent Classification[7]: C07D 487/08, A61K 31/551, A61P 25/00, 1/04

(21) International Application Number: PCT/SE2003/001276

(22) International Filing Date: 13 August 2003 (13.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0202465-1 14 August 2002 (14.08.2002) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ERNST, Glen** [US/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **PHILLIPS, Eifion** [GB/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US). **SCHMIESING, Richard** [US/US]; AstraZeneca Wilmington, P.O. Box 15437, Wilmington, DE 19850-5437 (US).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

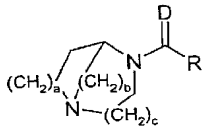
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/016616 A1

(54) Title: ARYL-SUBSTITUTED DIAZABICYCLOALKANES AS NICOTINIC ACETYLCHOLINE AGONISTS.



(57) Abstract: Nicotinic acetylcholine receptor agonists of formula I wherein a, b, c, D and R are as defined in the specification, enantiomers, pharmaceutically- acceptable salts, methods of making, pharmaceutical compositions containing and methods for using the same in the treatment or prophylaxis of psychotic disorders, intellectual impairment disorders, Alzheimer's disease, leaning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is a loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction, pain, ulcerative colitis or irritable bowel syndrome.

ARYL-SUSBSTITUTED DIAZABICYCLOALKANES AS NICOTINIC ACETYLCHOLINE AGONISTS.

Technical Field

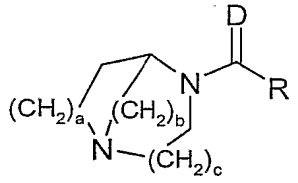
This invention relates to diazabicycloalkane amides or pharmaceutically-acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. The invention also relates to compounds active as nicotinic acetylcholine receptors (nAChRs) agonists.

Background of the Invention

The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

Disclosure of the Invention

The invention comprises compounds of formula I



I

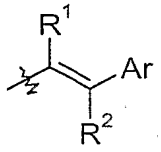
wherein:

a, b and c are each 1 or 2;

D is oxygen or sulfur, and

R is selected from moieties of formulae II, III or IV:

II



III

IV

wherein

R^1, and R^2 are independently selected from hydrogen, CN, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl or CO_2R^3;

Ar is phenyl, or

Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered fused aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered aromatic carbocyclic ring;

said Ar phenyl, heterocyclic rings or carbocyclic having 0, 1 or more substituents independently selected from hydrogen, CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OR^3, CO_2R^3 or NR^3R^4; where

R^3 and R^4 are independently at each occurrence selected from hydrogen, C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^5$, CO_2R^5, SO_2R^6, or

R^3, R^4 and N in combination in the substituent $-NR^3R^4$ is $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^5, or a bond; j is 2, 3 or 4 and k is 0, 1 or 2;

wherein

R^5 at each occurrence is independently selected from hydrogen, C_{1-4}alkyl, aryl, or heteroaryl, and

R^6 at each occurrence is independently selected from C_{1-4}alkyl, aryl, or heteroaryl.

Another embodiment of the invention comprises compounds wherein D is oxygen.

Yet another embodiment of the invention comprises compounds wherein a is 1, b is 2 and c is 1.

Still another embodiment of the invention comprises compounds wherein Ar is phenyl, or Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur.

Another embodiment of the invention comprises compounds wherein Ar is a phenyl, furanyl or thiophenyl.

Particular compounds of the invention are those wherein a is 1, b is 2, c is 1, D is oxygen, R^1 and R^2 are hydrogen and Ar is phenyl, or Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or Ar is an 8-, 9- or 10-

membered fused aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or Ar is an 8-, 9- or 10-membered aromatic carbocyclic ring.

Particular compounds of the invention are also those wherein Ar is selected from phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl, 2-furanyl or 3-furanyl, 2-thienyl or 3-thienyl, benzofuran-2-yl; benzofuran-3-yl, benzo[b]thiophen-2-yl or benzo[b]thiophen-3-yl.

Particular compounds of the invention are also those wherein Ar is substituted with one or more substituents independently selected from CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OR^3, CO_2R^3 or NR^3R^4.

Other particular compounds of the invention are:

(1,4-diazabicyclo[3.2.2]non-4-yl)(phenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3-fluorophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-fluorophenyl)methanone;

(3-chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(4-chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3,4-dichlorophenyl)methanone;

(3-bromophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(4-bromophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3-iodophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-iodophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-trifluoromethylphenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-methoxyphenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-trifluoromethoxyphenyl)methanone;

(5-chlorofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(5-bromofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(5-iodoofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(5-chlorothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(5-bromothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(5-iodoothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(naphthalen-2-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(benzofuran-2-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(benzo[b]thiophen-2-yl)methanone;

1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-phenylpropenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-phenylpropynone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-3-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-3-yl)propenone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(furan-2-yl)methanone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methoxyphenyl)-propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methylphenyl)propenone;
(1,4-diaza-bicyclo[3.2.2]non-4-yl)-(1H-indol-5-yl)-methanone;
(1,4-diaza-bicyclo[3.2.2]non-4-yl)-(methyl-1H-indol-2-yl)-methanone, and
(Z)-1-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-2-fluoro-3-phenyl-propenone.

Most particular compounds of the invention are those of the examples herein.

Each embodiment and particular form of the invention encompass all diastereoisomers, enantiomers and pharmaceutically-acceptable derivatives and salts of compounds thereof.

Pharmaceutically-acceptable derivatives include solvates and salts. For example, the compounds of formula I can form acid addition salts with acids, such as the conventional pharmaceutically-acceptable acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic acids.

Compounds of the invention are useful in the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial as well as in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders. Examples of such conditions, diseases or disorders are Alzheimers disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotinic addiction including that resulting

from exposure to products containing nicotine, pain, for ulcerative colitis and irritable bowel disease.

As used herein, unless otherwise indicated, "C_{1-4}alkyl" includes but is not limited to methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl moieties, whether alone or part of another group, C_{1-4}alkyl groups may be straight-chained or branched, and C_{3-4}alkyl groups include the cyclic alkyl moieties cyclopropyl and cyclobutyl. Alkyl groups referred to herein may have 1, 2 or 3 halogen substituents.

As used herein, unless otherwise indicated, "C_{2-4}alkenyl" includes but is not limited to 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.

As used herein, unless otherwise indicated, "C_{2-4}alkynyl" includes but is not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl.

As used herein, unless otherwise indicated, aryl refers to a phenyl ring which may have 1, 2 or 3 substituents selected from CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, OC_{1-4}alkyl, NH_2 and CO_2C_{1-4}alkyl.

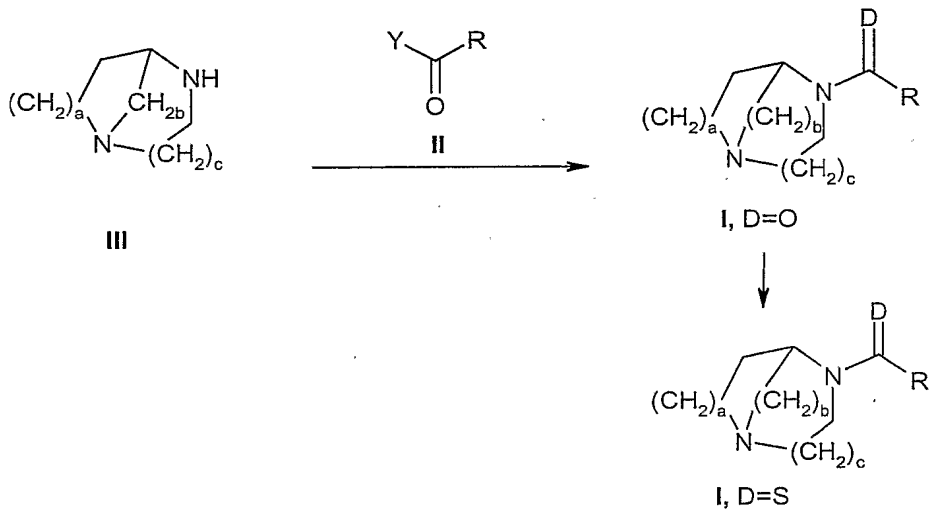
As used herein, unless otherwise indicated, heteroaryl refers to a 5- or 6-membered aromatic or heteroaromatic ring having 0, 1, 2 or 3 nitrogen atoms, 0 or 1 oxygen atom, and 0 or 1 sulfur atom, provided that the ring contains at least one nitrogen, oxygen, or sulfur atom. Heteroaryl moieties may have one or more substituents selected from CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, NH_2, CO_2H, OC_{1-4}alkyl and CO_2C_{1-4}alkyl.

As used herein, unless otherwise indicated, halogen refers to fluorine, chlorine, bromine, or iodine.

Methods of Preparation

In the reaction schemes and text that follow, D and R, unless otherwise indicated, are as defined above for formula I. The compounds of formula I may be prepared according to the methods outlined in Scheme 1.

Scheme 1



Compounds of formula I wherein D represents O may be prepared from compounds of formula III by reaction with a compound of formula II, wherein Y represents a suitable leaving group, using a suitable acylation procedure. Suitable leaving groups Y include: OH, halogen, Oalkyl, Oaryl, OCOalkyl, OCOaryl, azide. A suitable acylation procedure involves treatment of a compound of formula III with a compound of formula II at 0-120 °C in a suitable solvent. The presence of a base, or, when Y=OH, a coupling agent, may also be necessary for the reaction to occur. Suitable bases for the reaction include: 4-(*N,N*-dimethylamino)pyridine, pyridine, triethylamine, *N,N*-diisopropylethylamine. The preferred base is *N,N*-diisopropylethylamine. Suitable coupling agents when Y=OH include: carbodiimides, for example 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride; phosphonium reagents, for example benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; and uronium reagents, for example *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The preferred coupling agent is *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. Suitable solvents for the reaction include *N,N*-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, or chloroform. The preferred solvent is *N,N*-dimethylformamide. The reaction is preferably performed at a temperature of 0-50 °C, and most preferably at a temperature of 20-30 °C.

Compounds of formula I in which D represents S may be prepared from compounds of formula I in which D represents O by reaction with a suitable sulfide in a suitable solvent.

The preferred sulfides are phosphorus sulfides, in particular 4-methoxyphenyl-thionophosphine sulfide dimer ("Lawesson's Reagent"), and diphosphorus pentasulfide.

Suitable solvents for the reaction include aryl hydrocarbon solvents, for example toluene or xylene. The reaction is performed at a temperature of 0-200 °C, and preferably at a temperature of 50-180 °C.

It will be appreciated by one skilled in the art that certain optional aromatic substituents in the compounds of the invention may be introduced by employing aromatic substitution reactions, or functional group transformations to modify an existing substituent, or a combination thereof. Such reactions may be effected either prior to or immediately following the processes mentioned above, and are included as part of the process aspect of the invention. The reagents and reaction conditions for such procedures are known in the art. Specific examples of procedures which may be employed include, but are not limited to, electrophilic functionalisation of an aromatic ring, for example via nitration, halogenation, or acylation; transformation of a nitro group to an amino group, for example via reduction, such as by catalytic hydrogenation; acylation, alkylation or sulfonylation of an amino or hydroxyl group; replacement of an amino group by another functional group via conversion to an intermediate diazonium salt followed by nucleophilic or free radical substitution of the diazonium salt; or replacement of a halogen by another functional group for example via nucleophilic or catalysed substitution reactions.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere). Unless otherwise stated, the above described reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

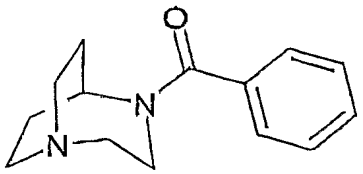
Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the

appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

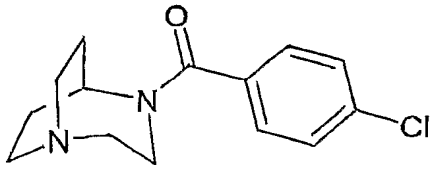
Example 1: (1,4-Diazabicyclo[3.2.2]non-4-yl)(phenyl)methanone



Benzoic acid (61 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 89 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to yield (1,4-diaza-bicyclo[3.2.2]non-4-yl)(phenyl)methanone (13 mg, 11%) as a tan waxy solid.

MS (APCI+) 231 $[M+1]^+$.

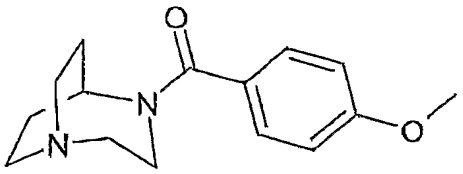
Example 2: (4-Chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone



4-Chlorobenzoic acid (79 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 89 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to yield (4-chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone (73 mg, 55%) as a tan oil.

MS (APCI+) 265/267 $[M+1]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.49 (2H, d), 7.40 (2H, d), 4.58-4.50 (1H, m), 3.83-3.68 (1H, m), 3.48-3.36 (1H, m), 3.02-2.75 (6H, m), 2.08-1.45 (4H, m).

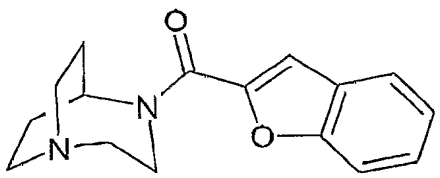
Example 3: (1,4-Diazabicyclo[3.2.2]non-4-yl)(4-methoxyphenyl)methanone



4-Methoxybenzoic acid (76 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (1,4-diazabicyclo[3.2.2]non-4-yl)(4-methoxyphenyl)methanone (13 mg, 10%) as a colorless resin.

MS (APCI+) 261 $[M+1]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (2H, d), 6.96 (2H, d), 4.62-4.40 (1H, m), 3.80 (2H, br s), 3.78 (3H, s), 2.99-2.76 (6H, m), 2.09-1.47 (4H, m).

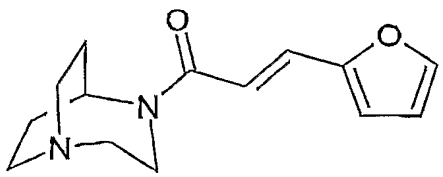
Example 4: (1,4-Diazabicyclo[3.2.2]non-4-yl)(benzofuran-2-yl)methanone



Benzofuran-2-carboxylic acid (81 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (1,4-diazabicyclo[3.2.2]non-4-yl)(benzofuran-2-yl)methanone (46 mg, 34%) as a yellow solid.

MS (APCI+) 271 $[M+1]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (1H, d), 7.65 (1H, d), 7.43 (1H, dd), 7.38-7.28 (2H, m), 4.59-4.38 (1H, m), 3.91-3.73 (2H, m), 3.00-2.85 (6H, m), 2.09-1.91 (2H, m), 1.83-1.64 (2H, m).

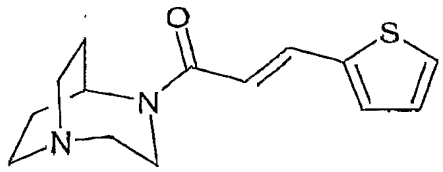
Example 5: (E)-1-(1,4-Diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone



(E)-3-Furan-2-yl-acrylic acid (69 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone (49 mg, 40%) as a beige solid.

MS (APCI+) 247 [M+1]+ ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.98-7.73 (1H, m), 7.42-7.23 (1H, m), 6.97-6.76 (2H, m), 6.63-6.53 (1H, m), 4.56-4.26 (1H, m), 3.80-3.66 (2H, m), 3.02-2.77 (6H, m), 1.97-1.53 (4H, m).

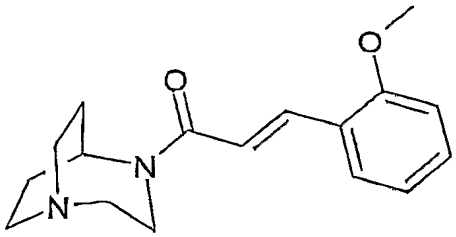
Example 6: (E)-1-(1,4-Diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone



(E)-3-Thiophen-2-yl-acrylic acid (77 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone (62 mg, 47%) as a colorless oil.

MS (APCI+) 263 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.73-7.55 (2H, m), 7.48-7.42 (1H, m), 7.15-7.01 (1H, m), 6.96-6.76 (1H, m), 4.56-4.31 (1H, m), 3.79-3.70 (2H, m), 2.99-2.77 (6H, m), 1.97-1.54 (4H, m).

Example 7: (E)-1-(1,4-Diazabicyclo[3.2.2]non-4-yl)-3-(2-methoxyphenyl)-propenone

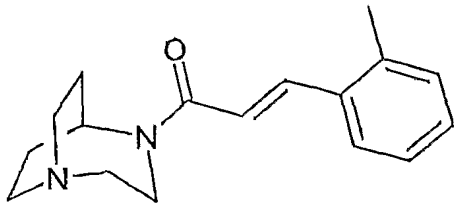


(E)-3-(2-Methoxyphenyl)acrylic acid (89 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-

dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methoxyphenyl)propenone (74 mg, 52%) as a yellow solid.

MS (APCI+) 287 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.97-7.67 (2H, m), 7.41-7.30 (1H, m), 7.23-6.92 (3H, m), 4.57-4.35 (1H, m), 3.85 (3H, s), 3.81-3.72 (2H, m), 3.02-2.78 (6H, m), 1.97-1.54 (4H, m).

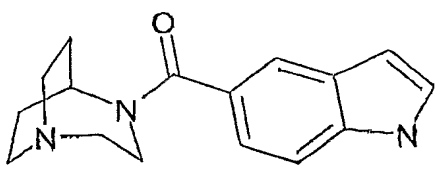
Example 8: (E)-1-(1,4-Diazabicyclo[3.2.2]non-4-yl)-3-(2-methylphenyl)propenone



(E)-3-(2-Methylphenyl)acrylic acid (81 mg, 0.50 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161 mg, 0.50 mL) and diisopropylethylamine (0.35 mL, 250 mg, 2.0 mmol) in dry N,N-dimethylformamide (2 mL) were stirred at ambient temperature for 20 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water (2x). The solvent was blown off with a stream of nitrogen to yield (E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methylphenyl)propenone (76 mg, 56%) as a colorless oil.

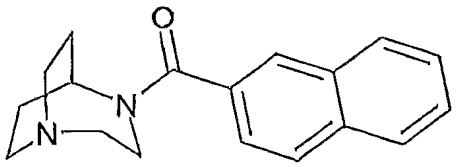
MS (APCI+) 271 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.83-7.64 (2H, m), 7.32-7.17 (3H, m), 7.16-6.96 (1H, m), 4.57-4.41 (1H, m), 3.83-3.72 (2H, m), 3.00-2.77 (6H, m), 2.37 (3H, s), 2.00-1.54 (4H, m).

Example 9: (1,4-Diaza-bicyclo[3.2.2]non-4-yl)-(1H-indol-5-yl)-methanone



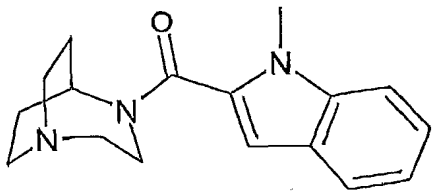
Indole-5-carboxylic acid (40 mg, 0.25 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (50 mg, 0.25 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (81 mg, 0.25 mmol) and diisopropylethylamine (0.17 mL, 129 mg, 1.0 mmol) in dry N,N-dimethylformamide (1.5 mL) were stirred at ambient temperature for 24 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* to yield 10 mg of product. The reaction mixture was chromatographed with 100% EtOAc to 90:10 EtOAc:7N NH_3/MeOH to give (1,4-diaza-bicyclo[3.2.3]non-4-yl)-(1H-indol-5-yl)-methanone (5 mg, 7%) as a pale yellow oil.
MS (APCI+) 270 $[M+1]^+$; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.67 (1H, s), 7.68 (1H, s), 7.35 (1H, d), 7.26-7.20 (2H, m), 6.56 (1H, s), 4.81 (1H, s), 3.67-3.66 (2H, m), 3.07-2.97 (6H, m), 2.13-2.00 (2H, m), 1.77 (3H, s).

Example 10: (1,4-Diaza-bicyclo[3.2.2]non-4-yl)-(naphthylene-2-yl)-methanone



2-Napthoic acid (43 mg, 0.25 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (50 mg, 0.25 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (81 mg, 0.25 mmol) and diisopropylethylamine (0.17 mL, 129 mg, 1.0 mmol) in dry N,N-dimethylformamide (1.5 mL) were stirred at ambient temperature for 24 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* to yield 50 mg of product. The reaction mixture was chromatographed with 100% EtOAc to 90:10 EtOAc:7N NH_3/MeOH to give (1,4-diaza-bicyclo[3.2.2]non-4-yl)-naphthalen-2-yl-methanone (46 mg, 66%) as a colorless oil.
MS (APCI+) 281 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.89-7.84 (4H, m), 7.61-7.46 (3H, m), 4.84 (1H, s), 3.59 (1H, s), 3.15-2.94 (7H, m), 2.18 (2H, s), 1.83 (2H, s) 1.66 (1H, s).

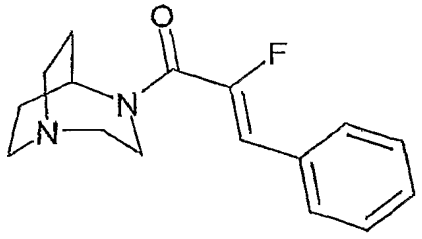
Example 11: (1,4-Diaza-bicyclo[3.2.2]non-4-yl)-(methyl-1H-indol-2-yl)-methanone



1-Methylindole-2-carboxylic acid (44 mg, 0.25 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (50 mg, 0.25 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (81 mg, 0.25 mmol) and diisopropylethylamine (0.17 mL, 129 mg, 1.0 mmol) in dry N,N-dimethylformamide (1.5 mL) were stirred at ambient temperature for 24 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* to yield 54 mg of product. The reaction mixture was chromatographed with 100% EtOAc to 90:10 EtOAc:7N NH_3/MeOH to give (1,4-diaza-bicyclo[3.2.2]non-4-yl)-(1-methyl-1H-indol-2-yl)-methanone (48 mg, 68%) as a colorless oil.

MS (APCI+) 284 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62 (1H, d), 7.39-7.26 (2H, m), 7.16 (1H, dd) 6.56 (1H, s), 4.80 (1H, s), 3.86-3.77 (5H, m), 3.07-3.02 (7H, m), 2.04 (2H, s), 1.81 (2H, s) 1.66 (1H, s).

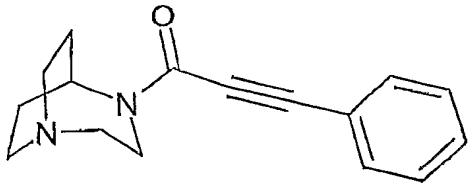
Example 12: (Z)-1-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-2-fluoro-3-phenyl-propenone



α-fluorocinnamic acid (42 mg, 0.25 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (50 mg, 0.25 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (81 mg, 0.25 mmol) and diisopropylethylamine (0.17 mL, 129 mg, 1.0 mmol) in dry N,N-dimethylformamide (1.5 mL) were stirred at ambient temperature for 24 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over Na_2SO_4. After filtration,

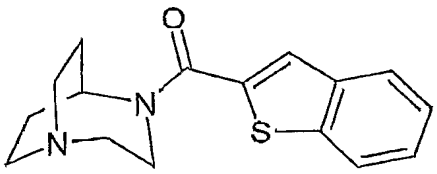
the solvent was removed *in vacuo* to yield 61 mg of product. The reaction mixture was chromatographed with 100% EtOAc to 90:10 EtOAc:7N NH_3/MeOH to give (Z)-1-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-2-fluoro-3-phenyl-propenone (54 mg, 78%) as a colorless oil. MS (APCI+) 275 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 (2H, d), 7.40-7.29 (3H, m), 6.49 (1H, d), 4.62 (1H, s), 3.75 (2H, s), 3.15-2.95 (7H, m), 2.06-2.02 (2H, m), 1.79 (2H, s).

Example 13: 1-(1,4-Diaza-bicyclo[3.2.2]non-4-yl)-3-phenyl-propynone



Phenylpropionic acid (37 mg, 0.25 mmol), 1,4-diaza-bicyclo[3.2.2]nonane dihydrochloride (50 mg, 0.25 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 0.25 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (81 mg, 0.25 mmol) and diisopropylethylamine (0.17 mL, 129 mg, 1.0 mmol) in dry N,N-dimethylformamide (1.5 mL) were stirred at ambient temperature for 24 h. The reaction mixture was poured into 1N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate layer was washed with 1N NaOH (1x), water (4x), brine (1x), and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* to yield 45 mg of product. The reaction mixture was chromatographed with 100% EtOAc to 90:10 EtOAc:7N NH_3/MeOH to give 1-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-3-phenyl-propynone (38 mg, 59%) as a colorless oil.
MS (APCI+) 255 [M+1]+; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.61-7.51 (2H, m), 7.45-7.33 (3H, m), 4.68-4.62 (1H, m), 4.00 (1H, t), 3.86 (1H, t), 3.17-2.94 (6H, m), 2.12-1.99 (2H, m), 1.88-1.68 (3H, m).

Example 13: (1,4-diazabicyclo[3.2.2]non-4-yl)(benzo[b]thiophen-2-yl)methanone dihydrochloride.



To a stirred mixture of 1,4-diazabicyclo[3.2.2]nonane dihydrochloride (100 mg, 0.51 mmol), triethylamine (0.3 mL) and a catalytic amount of N,N-dimethylaminopyridine in dry

THF (2.5 mL) at ambient temperature was added a solution of benzo[b]thiophene-2-carbonyl chloride in dry THF (0.5 mL). After stirring at ambient temperature for 2 hours the mixture was partitioned between water and ethyl acetate, the organic phases recovered, washed with water and brine, then dried over sodium sulfate. The product obtained by concentration of the dried organic phases was subjected to silica gel chromatography, eluting with an ammoniated-chloroform to 5% methanol/chloroform gradient to give the title compound as a free base. The eluted material was dried to a solid. The solid was taken up in methanol, made acidic with HCl in ether (2.0 M), diluted with ether and allowed to stand. The resulting salt was collected, washed, and dried *in vacuo* to give the title compound as a white solid (55.0 mg). MS (ES+) 287 (MH+).

Pharmaceutical compositions

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, enantiomers thereof, and pharmaceutically-acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

– for tablets and dragees: lactose, starch, talc, stearic acid;

– capsules: tartaric acid or lactose;

– for injectable solutions: water, alcohols, glycerin, vegetable oils;

– for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition, which comprises mixing the ingredients.

One aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

Compounds to be used according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the α_7 nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are or are also agonists of the α_4 nAChR subtype. Therefore, compounds which are selective for the α_7 nAChR subtype are preferred. The use of compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at α_7 nAChR subtype

^{125}I-α-Bungarotoxin (BTX) binding to rat hippocampal membranes.

Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 xg, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 xg, washed, and resuspended in HB. Membranes (30–80 μg) were incubated with 5 nM [^{125}I]α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 hours at 21 °C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 μM (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α_4 nAChR subtype

[^{3}H]-(–)-nicotine binding.

Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [^{125}I]α-BTX binding assay, centrifuged for 20 minutes at 12,000 xg, washed twice, and then resuspended in HB containing 100 μM diisopropyl fluorophosphate. After 20 minutes at 4 °C, membranes (approximately 0.5 mg) were incubated with 3 nM [^{3}H]-(–)-nicotine, test drug, 1 μM atropine, and either 2 mM $CaCl_2$ or 0.5 mM EGTA for 1 hour at 4 °C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 μM carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

IC_{50} values and pseudo Hill coefficients (nH) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding KD values of 1.67 and 1.70 nM for the ^{125}I-α-BTX and [^{3}H]-(–)-nicotine ligands respectively. Ki values were estimated using the general Cheng-Prusoff equation:

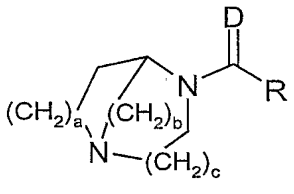
$$K_i=[IC_{50}]/((2+([ligand]/[K_D])^n)^{1/n}-1)$$

where a value of n=1 was used whenever $^{n}H<1.5$ and a value of n=2 was used when $^{n}H\geq1.5$. Samples were assayed in triplicate and were typically ±5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 10 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

CLAIMS

1. A compound of formula I:



I

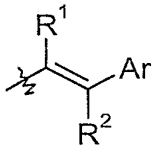
wherein:

a, b and c are each 1 or 2;

D is oxygen or sulfur, and

R is selected from moieties of formulae II, III or IV:

II



III

IV

wherein

R^1, and R^2 are independently selected from hydrogen, CN, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl or CO_2R^3;

Ar is phenyl, or

Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered fused aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered aromatic carbocyclic ring,

wherein said phenyl, heterocyclic rings or carbocyclic rings have 0, 1 or more substituents independently selected from hydrogen, CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OR^3, CO_2R^3 or NR^3R^4; where

R^3 and R^4 are independently at each occurrence selected from hydrogen, C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^5$, CO_2R^5, SO_2R^6, or

R^3, R^4 and N in combination in the substituent $-NR^3R^4$ is $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^5, or a bond; j is 2, 3 or 4 and k is 0, 1 or 2;

wherein

R^5 at each occurrence is independently selected from hydrogen, C_{1-4}alkyl, aryl, or heteroaryl, and

R^6 at each occurrence is independently selected from C_{1-4}alkyl, aryl, or heteroaryl;

or an enantiomer or pharmaceutically-acceptable salt thereof.

2. A compound according to Claim 1, wherein D is oxygen.

3. A compound according to Claim 1, wherein a is 1, b is 2 and c is 1,

or an enantiomer or pharmaceutically-acceptable salt thereof.

4. A compound of Claim 1, wherein

Ar is phenyl, or

Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1 or 2 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur;

or an enantiomer or pharmaceutically-acceptable salt thereof.

5. A compound according to Claim 4, wherein Ar is a phenyl, furanyl or thiophenyl; or an enantiomer or pharmaceutically-acceptable salt thereof.

6. A compound according to Claim 1, wherein:

a is 1;

b is 2;

c is 1;

D is oxygen;

R^1 and R^2 are hydrogen;

Ar is phenyl, or

Ar is a 5- or 6-membered aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered fused aromatic heterocyclic moiety having 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur where not more than one of said heteroatoms is oxygen or sulfur, or

Ar is an 8-, 9- or 10-membered aromatic carbocyclic ring;

or an enantiomer or pharmaceutically-acceptable salt thereof.

7. A compound according to Claim 1, wherein:

Ar is selected from phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl, 2-furanyl or 3-furanyl, 2-thienyl or 3-thienyl, benzofuran-2-yl; benzofuran-3-yl, benzo[b]thiophen-2-yl or benzo[b]thiophen-3-yl;

or an enantiomer or pharmaceutically-acceptable salt thereof.

8. A compound according to Claim 1, wherein:

Ar is substituted with one or more substituents independently selected from CN, NO_2, CF_3, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OR^3, CO_2R^3 or NR^3R^4;

or an enantiomer or pharmaceutically-acceptable salt thereof.

9. A compound according to Claim 1 selected from:

(1,4-diazabicyclo[3.2.2]non-4-yl)(phenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3-fluorophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-fluorophenyl)methanone;

(3-chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(4-chlorophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3,4-dichlorophenyl)methanone;

(3-bromophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(4-bromophenyl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(3-iodophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-iodophenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-trifluoromethylphenyl)methanone;

(1,4-diazabicyclo[3.2.2]non-4-yl)(4-methoxyphenyl)methanone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(4-trifluoromethoxyphenyl)methanone;
(5-chlorofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(5-bromofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(5-iodoofuran-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(5-chlorothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(5-bromothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(5-iodoothiophen-2-yl)(1,4-diazabicyclo[3.2.2]non-4-yl)methanone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(naphthalen-2-yl)methanone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(benzofuran-2-yl)methanone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(benzo[b]thiophen-2-yl)methanone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-phenylpropenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-phenylpropynone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-3-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone;
1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-3-yl)propenone;
(1,4-diazabicyclo[3.2.2]non-4-yl)(furan-2-yl)methanone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(furan-2-yl)propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(thiophen-2-yl)propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methoxyphenyl)-propenone;
(E)-1-(1,4-diazabicyclo[3.2.2]non-4-yl)-3-(2-methylphenyl)propenone;
(1,4-diaza-bicyclo[3.2.2]non-4-yl)-(1H-indol-5-yl)-methanone;
(1,4-diaza-bicyclo[3.2.2]non-4-yl)-(methyl-1H-indol-2-yl)-methanone, and
(Z)-1-(1,4-diaza-bicyclo[3.2.2]non-4-yl)-2-fluoro-3-phenyl-propenone,

or an enantiomer or pharmaceutically-acceptable salt thereof.

10. A compound according to any one of Claims 1 to 10, for use in therapy.

11. A compound according to any one of Claims 1 to 10, for use as a medicament.

12. Use of a compound as defined in any one of claims 1 to 10, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders, intellectual impairment disorders, human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial, Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, ulcerative colitis or irritable bowel syndrome.

13. A method of treatment or prophylaxis of psychotic disorders, intellectual impairment disorders, human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial, Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis which method comprises administering a therapeutically effective amount of a compound as defined in any one of Claims 1 to 10.

14. A pharmaceutical composition comprising a compound of formula I, as defined in any one of claims 1 to 10, together with at least one pharmaceutically-acceptable excipient or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01276

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 487/08, A61K 31/551, A61P 25/00, A61P 1/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1990:423956, document no. 113:23956, Pfizer Inc., "Preparation of diazabicyclononanes as intermediates for antibacterial quinolones", & US,A,4895943,19900123 --	1-7,9
X	STN International, file CAPLUS, CAPLUS accession no. 1966:27623, document no. 64:27623, Merck & Co., Inc. "1,3-Ethanopiperazine and derivatives", & NL,65001367,19650804 --	1-2,4-5,7

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 2003	04 -12- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer PER RENSTRÖM/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01276

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1964:454808, document no. 61:54808, Rubtsov, M. V. et al, "Beckmann rearrangement in the heterocyclic series. Rearrangement of oximes of 3-quinuclidone and 1-azabicyclo [3.2.1]6-octanone", & Zh. Obshch. Khim. (1964), 34 (7), 2222-6	1-2,4-5,7
X	WO 0058311 A1 (SANOFI-SYNTHELABO), 5 October 2000 (05.10.00), abstract, page 7, table, page 8, line 4 - line 8, page 9, line 7 - page 10, line 4	1-14
X	EP 1219622 A2 (PFIZER PRODUCTS INC.), 3 July 2002 (03.07.02), abstract, page 1, line 19 - page 7, line 30; example, claims	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01276

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.
PCT/SE 03/01276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0058311 A1	05/10/00	AT 232865 T	15/03/03
		AU 3301800 A	16/10/00
		DE 60001451 D	00/00/00
		DK 1165559 T	10/06/03
		EP 1165559 A,B	02/01/02
		SE 1165559 T3	
		FR 2791678 A,B	06/10/00
		JP 2002540208 T	26/11/02
		SI 1165559 T	00/00/00
EP 1219622 A2	03/07/02	BR 0106462 A	24/09/02
		CA 2366268 A	29/06/02
		JP 2002255965 A	11/09/02
		US 2002086871 A	04/07/02
		US 2003119837 A	26/06/03